REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Claim 1 has been amended. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. 102

Claim 1 has been rejected under 35 U.S.C. 102(a) as being anticipated by Chamberlain et al. (1998). The Examiner suggests that this reference teaches administration of methotrexate to patients with leptomeningeal metastases presenting with radiculopathy, wherein the dose of methotrexate is administered intraventricularly and is a dose of 2 mg daily (total dose of 40 mg). The Examiner suggests that because Chamberlain et al. teach the same composition of methotrexate in the same dose (less than 3 mg/kg) to be useful in the treatment of leptomeningeal metastases with radiculopathy, that methotrexate would inherently be treating the radiculopathy, whether explicitly recognized or not. Further, the Examiner suggests that the administration of methotrexate intraventricularly overlaps with the administration route of the invention as claimed, such that Chamberlain et al.

anticipates the claimed invention. Applicants respectfully disagree with the Examiner's analysis and conclusions regarding this reference.

At the outset, claim 1 has been amended to recite that local administration into the back of the animal is intrathecal administration, as is defined in the specification as filed at page 5, and acknowledged by the Examiner.

Chamberlain et al. (1998) disclose only the intraventricular administration of methotrexate, as is discussed by the Examiner. Contrary to the Examiner's assertion, however, intraventricular administration of a drug is not the same as intrathecal administration and will not produce a local concentration of active drug in the spinal cord area that is anywhere near the same concentration as would be achieved with intrathecal administration. This is because, as taught in basic human anatomy and physiology texts (e.g., *Human Anatomy and Physiology*, Second Edition, Elaine N. Marieb (editor), Benjamin Cummings Publishing: Redwood City, CA, pages 404-405, starting at the second column on page 404) the circulation of cerebrospinal fluid through the brain ventricles is designed such that only some of

the cerebrospinal fluid from the ventricles circulates into the central canal of the spinal cord. As is taught in this text, "most enters the subarachnoid space" (see page 404, second column, line 3-4 of second paragraph). Therefore, since intraventricular injection of methotrexate as taught by Chamberlain et al. (1998) would result in only a small amount of circulation of the injected drug, via the cerebrospinal fluid, into the spinal cord, the concentration of methotrexate achieved would not be expected by one of skill in the art to be as high as could be achieved through direct administration into the spinal cord area via intrathecal administration. The subarachnoid space, as shown in Figure 12.20 on page 404 of the text cited above, is not the area touched through intrathecal administration. Thus, this fact, combined with the fact that nowhere does the cited reference teach or suggest use of methotrexate intrathecally at any dose for relief of pain indicates that this reference does not teach or suggest the method of the instant invention. In order to anticipate an invention, the cited reference must teach each and every limitation of the claims (MPEP 2131). Accordingly, this

reference cannot anticipate the claims as amended. Withdrawal of this rejection is respectfully requested.

II. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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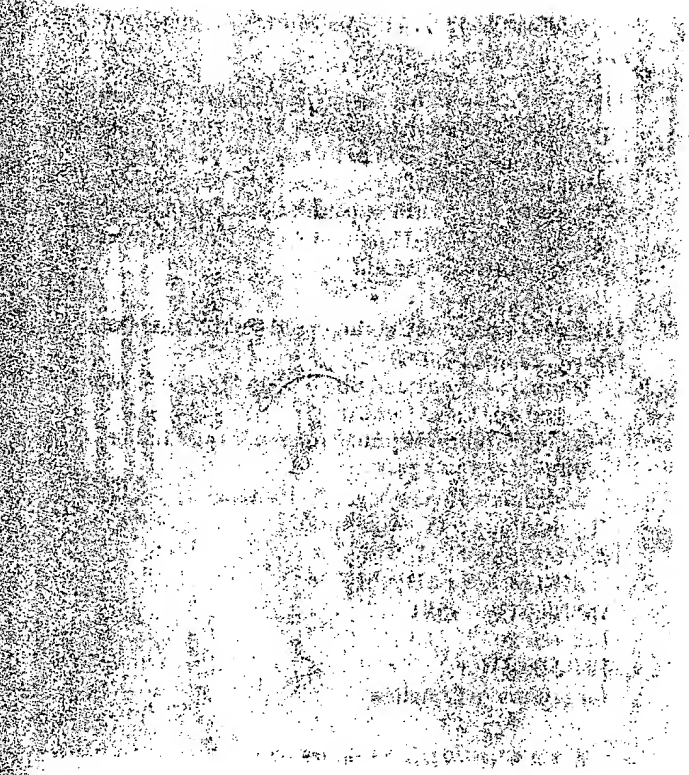

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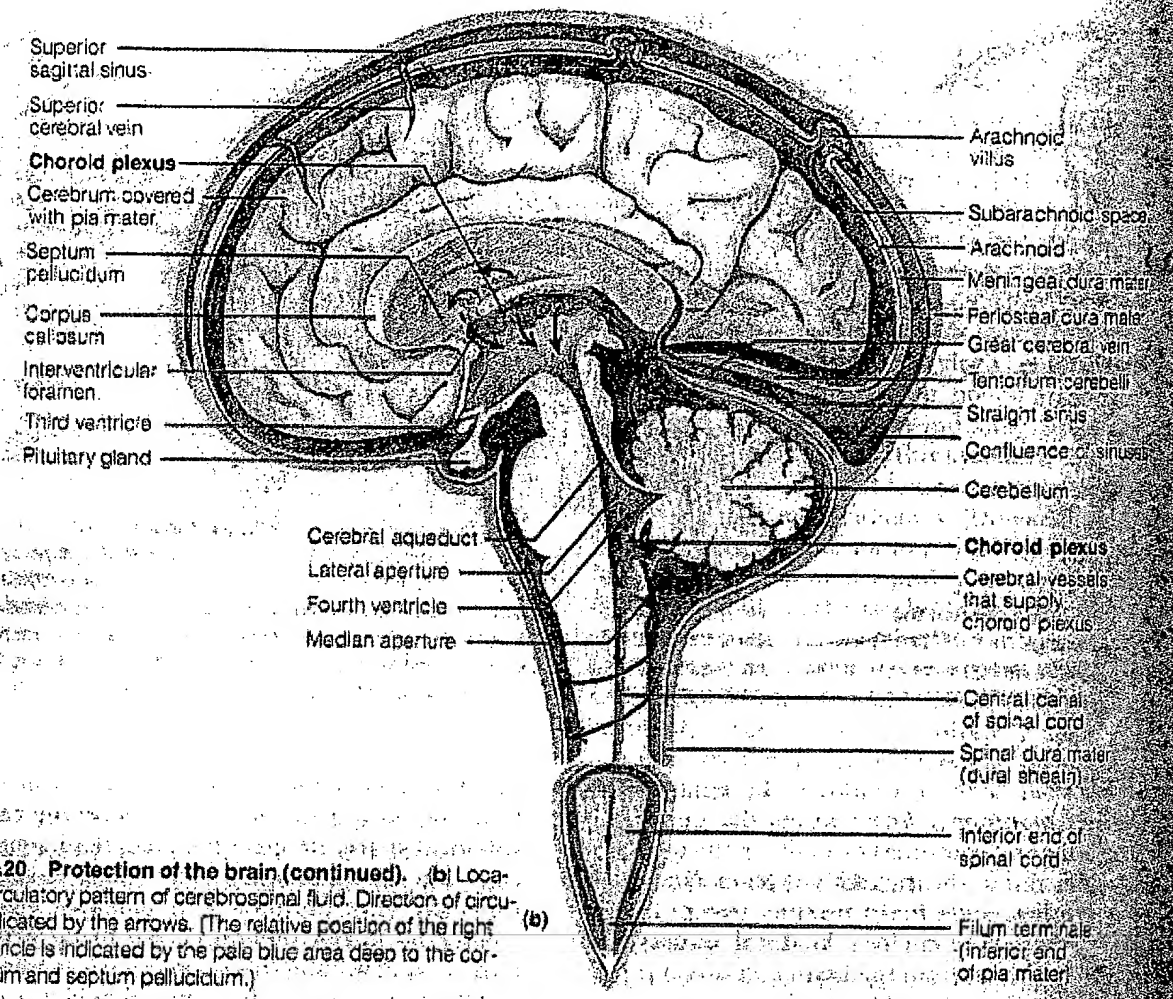

Figure 12.20 Protection of the brain (continued). (b) Location and circulatory pattern of cerebrospinal fluid. Direction of circulation is indicated by the arrows. (The relative position of the right lateral ventricle is indicated by the pale blue area deep to the corpus callosum and septum pellucidum.)

Cerebrospinal Fluid

Cerebrospinal fluid (CSF), found in and around the brain and spinal cord, forms a liquid cushion that gives buoyancy to the CNS organs. By floating the jellylike brain, the CSF effectively reduces brain weight by 97% and prevents the brain from crushing under its own weight. CSF also protects the brain and spinal cord from blows and other trauma. Additionally, although the brain has a rich blood supply, cerebrospinal fluid helps to nourish the brain.

CSF is a watery "broth" similar in composition to blood plasma, from which it arises. However, it contains less protein and more vitamin C, and its ion concentration is different. For example, CSF contains more sodium, chloride, magnesium, and hydrogen ions than blood plasma, and fewer calcium and potassium ions. CSF composition, particularly its pH, is important in the control of cerebral blood flow and breathing, as described in later chapters. CSF also transports hormones along the ventricular channels.

The **choroid plexuses** that hang from the roof of each ventricle (Figure 12.20b) form CSF. These plexuses are frond-shaped clusters of capillaries (*b*[illegible] interwoven) enclosed by ciliated epithelial cells[illegible] are continuous with the ependymal cells lining the ventricles. Although the capillaries of the choroid plexuses are fairly permeable and tissue fluid filters continuously from the bloodstream, the choroid plexus epithelial cells are joined by tight junctions and have ion pumps that allow them to modify the filtrate by actively transporting only certain ions across their membranes into the CSF pool. This sets up ionic gradients that cause water to diffuse into the ventricles as well. In adults, the total CSF volume of about 150 ml (about half a cup) is replaced every 4 hours, hence 900–1200 ml of CSF are formed daily. The choroid plexuses also help to cleanse the CSF by removing waste products and other unnecessary solutes.

Once produced, CSF moves freely through the ventricles. Some CSF circulates from the ventricles into the central canal of the spinal cord, but most enters the subarachnoid space via the lateral and medial apertures in the walls of the fourth ventricle

(Figure 12.20b). The constant motion of the CSF is aided by the cilia of the ependymal cells lining the ventricles. In the subarachnoid space, CSF bathes the outer surfaces of the brain and cord and then returns to the blood in the dural sinuses via the arachnoid villi.

Ordinarily, CSF is produced and drained at a constant rate. However, if something (such as a tumor) obstructs its circulation and/or drainage, it begins to accumulate and exert pressure on the brain. This condition is called *hydrocephalus* ("water on the brain"). Hydrocephalus in a newborn baby causes its head to enlarge; this is possible because the skull bones have not yet fused. In adults, however, hydrocephalus is more likely to result in brain damage because the skull is rigid and hard, and accumulating fluid compresses the blood vessels serving the brain and crushes the soft nervous tissue. Hydrocephalus is treated by inserting a shunt in the ventricles that drains off the excess fluid into a vein in the neck. ■

Blood-Brain Barrier

The **blood-brain barrier** is a protective mechanism that helps ensure that the brain's environment remains stable. No other body tissue is so absolutely dependent on a constant internal milieu as is the brain. In other body regions, the extracellular concentrations of hormones, amino acids, and ions are in constant flux, particularly after eating or exercise. If the brain were exposed to such chemical variations, the neurons would fire uncontrollably, because some hormones and amino acids serve as neurotransmitters and certain ions (particularly potassium) modify the threshold for neuronal firing.

Blood-borne substances within the brain's capillaries are separated from the extracellular space and neurons by (1) the continuous endothelium of the capillary wall; (2) a relatively thick basal lamina surrounding the external face of the capillary; and to a limited extent (3) the bulbous "feet" of the astrocytes that cling to the capillaries. The capillary endothelial cells are almost "seamlessly" joined all around by *tight junctions* (see Chapter 20, p. 636), making them the least permeable capillaries in the entire body. This relative impermeability of brain capillaries constitutes most (if not all) of the blood-brain barrier. Although it was formerly assumed that the astrocytes contribute to the blood-brain barrier, the electron microscope has revealed that their end feet are too far apart to form any true seal. It now appears that the major role of the astrocyte end feet is to provide the signals that stimulate the endothelial cells of the brain capillaries to form the tight junctions characteristic of the blood-brain barrier.

The blood-brain barrier is a selective, rather than an absolute, barrier. Nutrients, such as glucose, essential amino acids, and some electrolytes, move passively by facilitated diffusion through the endothelial cell membranes. Blood-borne metabolic wastes, such as urea and creatinine, as well as proteins, certain toxins, and most drugs, are prevented from entering brain tissue. Small nonessential amino acids and potassium ions not only are prevented from entering the brain, but also are actively pumped from the brain across the capillary endothelium.

The barrier is ineffective against fats, fatty acids, oxygen and carbon dioxide, and other fat-soluble molecules that diffuse easily through all plasma membranes. This explains why blood-borne alcohol, nicotine, and anesthetics can affect the brain.

The structure of the blood-brain barrier is not completely uniform. As noted above, the capillaries of the choroid plexuses are very porous, but the epithelial cells surrounding them have tight junctions. In some brain areas, the blood-brain barrier is entirely absent and, in such areas, the capillary endothelium is quite permeable, allowing blood-borne molecules easy access to the neural tissue. One such region is the vomiting center of the brain stem, which monitors the blood for poisonous substances. Another is in the hypothalamus, which regulates water balance, body temperature, and many metabolic activities; lack of a blood-brain barrier here is essential to allow the hypothalamus to sample the chemical composition of the blood. The blood-brain barrier is incompletely developed in newborn and premature infants, and potentially toxic substances can readily enter the CNS and cause problems not seen in adults.

Injury to the brain, whatever the cause, may cause a localized breakdown of the blood-brain barrier. Most likely, this reflects some change in the capillary endothelial cells or their tight junctions. This supposition is borne out by a new procedure that infuses a concentrated solution of mannitol (sugar) prior to infusing chemotherapeutic drugs. The mannitol causes the capillary endothelial cells to shrink, opening up gaps between their tight junctions that allow the drugs to breach the blood-brain barrier and gain access to brain tumors. ■

Homeostatic Imbalances of the Brain

Brain dysfunctions are unbelievably varied and extensive. We have mentioned some of them already, and we will discuss developmental problems in the final section of the chapter. Here, we will focus on traumatic brain injuries and degenerative disorders.

Traumatic Brain Injuries

Head injuries are the leading cause of accidental death in the USA. Consider, for example, what hap-